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(54) Title of the Invention: A Topical Skin Agent

(57) [Abstract]

[Objective] To provide a topical skin agent that has superior effectiveness in color lightening and beautifying and whitening the skin in conditions of pigment deposition after sunburn, blotches, freckles and melasma and that is of superior safety.

[Structure] A topical skin agent in which an extract of Copaiba (scientific name: Copaifera Leguminosae) is compounded.

[Claims]

[Claim 1] A topical skin agent characterized in that an extract of Copaiba (scientific name: Copaifera Leguminosae) is compounded.

[Claim 2] A topical skin agent as described in Claim 1 in which the compounding quantity of the extract of Copaiba of this invention is 0.005 to 20.0 parts by weight.

[Claim 3] A topical skin agent as described in Claim 1 or 2 which is a beautifying and whitening agent.

[Detailed Description of the Invention]

[0001]

[Field of Industrial Use] This invention relates to a topical skin agent that inhibits production of melanin and that is effective in the prevention and improvement of pigment deposition after sunburn and of blotches, freckles and melasma as a result of compounding the extract of Copaiba of this invention.

[0002]

[Prior Art and Problems the Invention is Intended to Solve] There are a number of points about the mechanism of development of skin blotches and other conditions that are unclear. In general, it is thought that the pigment melanin is formed because of hormone abnormalities and stimulation by ultraviolet rays from sunlight and that abnormal deposition of it in the skin occurs. The methods that are used for the treatment of these blotches and nevi include methods in which substances that inhibit melanin production, for example, in which large volumes of vitamin C are administered or glutathione is injected or methods in which kojic acid, L ascorbic acid and derivatives thereof (fatty acids, sulfuric acid, phosphoric acid esters, etc.), cysteine or glutathione or derivatives thereof are applied locally in the forms of ointments, creams and lotions. In Europe and the United States, hydroquinone preparations are used as medicinal drug products.

[0003]

[Problems the Invention Is Intended to Solve] However, these compounds, except for hydroquinone, manifest their effects extremely slowly, for which reason their beautifying and whitening effect in is not always sufficient. On the other hand, the effect of hydroquinone appears for a time. However, because sensitization occurs to it, its use is generally not permitted. Accordingly, in order to increase its safety, attempts have been made to convert it to a monoester of a higher fatty acid or to an alkyl monoether (Japanese Patent Application Early Disclosure No. 58-154507 [1983]). However, because esters are broken down by hydrolytic enzymes in the body, it is hard to say that they are safe. Further, ethers have not been found to be satisfactory in terms of safety.

[0004]

[Means for Solving the Problems] Therefore, the inventors studied the effects of a wide range of substances in inhibiting melanin production for the purpose of solving these problems. As a result, they perfected this invention by discovering that extracts of Copaiba (scientific name: Copaifera Leguminosae) have a melanin production inhibiting action. There have been no reports on the melanin production inhibiting action of extracts of Copaiba and nothing whatsoever is known about their application in beautifying and whitening agents. The inventors perfected this invention on the basis of the information described above.

[0005] Specifically, this invention is a topical skin agent characterized in that an extract of Copaiba (scientific name: Copaifera Leguminosae) is compounded in it.

[0006] We shall now present a detailed description of the structure of this invention. Copaiba, which is used in this invention, is a plant that grows in arid meadows and pastures in the Andes. The extracts that are used in this invention are obtained by immersing the entire Copaiba plant, including the leaves, stems and fruit of the plant, in an extraction solvent and subjecting them to heating and refluxing, after which the product is filtered and concentrated. Any extraction solvent may be used as long as it is a solvent that is ordinarily used in extraction. In particular, organic solvents including alcohols such as methanol and ethanol, water-containing alcohols and acetone and ethyl acetate can be used individually or in combination.

[0007] The quantity of Copaiba extract compounded in this invention is 0.005 to 20.0 weight %, and, preferably, 0.01 to 10.0 weight %, as dry matter in the total quantity of topical agent. When it is less than 0.005 weight %, the effect of this invention is not sufficiently manifested. When it exceeds 20.0 weight %, it is difficult to prepare the agent. This is not desirable. Moreover, there is no further increase in effect as the amount compounded increases over 10.0 weight %.

[0008] In addition to the aforementioned essential components, components that are ordinarily used in topical skin agents such as cosmetic drug products and medicinal drug products, for example, other beautifying-whitening agents, moisturizing agents, antioxidants, oleaginous components, ultraviolet ray absorbents, surfactants, thickeners, alcohols, powdered components, colorants, aqueous components, water and various types

of skin nutrients can be compounded appropriately as required in the skin topical agent of this invention.

[0009] In addition, metal blocking agents such as disodium edetate, trisodium edetate, sodium citrate, sodium polyphosphate, sodium metaphosphate and gluconic acid, drug preparations of caffeine, tannin, verapamil, tranexamic acid and derivatives thereof, licorice extracts, grabrizine [phonetic*], hot water extract of fire thorn fruit, various raw drugs, tocopherol acetate and glycyrrhizinic acid and derivatives or salts thereof, beautifying-whitening agents such as vitamin C, magnesium ascorbate phosphate, ascorbic acid glucoside, arbutin and kojic acid and saccharides such as glucose, fructose, mannose, sucrose and trehalose can be compounded appropriately.

[0010] The topical skin agent of this invention may be any type of preparation as long as it is one conventionally used for topical skin agents, including, for example, an ointment, a cream, an emulsion, a lotion, a pack or a bathing agent.

[0011] Next we shall describe this invention in greater detail by means of examples. However, this invention is not limited by them. The quantities compounded are weight %. Prior to presenting the examples, we shall describe the methods of testing for the melanin inhibiting effect and the beautifying-whitening effect of the plant extracts of this invention.

[0012] Test Methods and Results Thereof

1. Preparation of test materials

50 g of the stems and branches of Copaiba were immersed for 1 week at room temperature in ethanol, the extract solution was concentrated and 11.5 g of ethanol extract was obtained. This extract was dissolved in 1% DMSO, the solution was diluted to adjust its concentration and the following tests were performed using this solution.

[0013] 2. Cell culture method

Cultured cells of B16 melanoma of mouse origin were used. They were cultured in Eagle's MEM culture medium containing 10% FBS and theophylline (0.09 mg/ml) at 37°C in a CO_2 incubator (95% air, 5% carbon dioxide). After culturing for 24 hours, test material solution was added to give a final concentration (converted concentration for dry extract) of 10^{-2} to 10^{-5} weight % and culturing was continued for an additional 3 days. Visual evaluations of the quantity of melanin production and determinations of tyrosinase inhibiting effect were made by the methods described below.

[0014] 3. Visual determination of melanin quantity

A diffusion plate was placed on the cover of the well plate, the quantity of melanin inside the cells was observed with an invert microscope and a comparison was made with the case of a test material (reference) to which Copaiba extract had not been added. Table 1 shows the results. As the reference example, the same test as described above was performed with Lamium sp. [dead nettle] (Labiatae, genus Lamium), which is known to have a melanin production inhibiting action. The results are also shown in Table 1. In the table, toxicity indicates cytotoxicity.

[0015] < Evaluation Criteria >

O: white (quantity of melanin)

Δ somewhat white (quantity of melanin)

X: reference (quantity of melanin)

[0016]

[Table 1]

Test	Melanin Production Visual Evaluation			
Tyrosinase Activity Inhibition Rate (%)	10^{-5}	10^{-4}	10^{-3}	10^{-2}
Concentration (weight %)	**x**	**x**	**x**	**o**
Copaiba extract	x	x	x	x
Lamium extract				

[0017] 4. Beautifying-whitening Effect Test

[Test Method] Skin on the inner side of the upper arm of 40 subjects who had been exposed to summer sunlight for 4 hours (two hours a day, two days) was the object of the test. Each test material was applied once in the morning and evening over a four week period from day 5 after the day of exposure to the sunlight. The panel was divided into groups of 8 subjects, to give 5 groups and the tests were conducted with the formulation indicated below.

(Alcohol phase)	
95% ethyl alcohol	55.0 weight %
Polyoxyethylene (25 mol) hardened castor oil ether	2.0
Antioxidant - preservative	suitable quantity
Fragrances	suitable quantity
Drug (shown in Table 2)	
(Aqueous phase)	
Glycerol	5.0
Sodium hexametaphosphate	suitable quantity
Ion exchange water	Remainder

*[Translator's Note: Transliterated phonetically from the Japanese As such, the source may differ from other transiterations.]

< Preparation Method > The aqueous phase and the alcohol phase were prepared separately, after which the two were mixed and solubilized.

[0018] Evaluation method. The color lightening effect after use was evaluated on the basis of the following evaluation criteria.

< Evaluation criteria >

◎ Case in which marked effectiveness and effectiveness was exhibited in more than 80% of the test subjects

O: Case in which marked effectiveness and effectiveness was exhibited in 50% to 80% of the test subjects

Δ: Case in which marked effectiveness and effectiveness was exhibited in 30% to 50% of the test subjects

X: Case in which marked effectiveness and effectiveness was exhibited in less than 30% of the test subjects

[0019] Test materials comprised of the compounding compositions indicated in the test methods described above and the whitening-beautifying effects as presented in Table 2 were compared. The results are shown in Table 2.

[0020]
[Table 2]

Drug	Compounded Amount (weight %)	Effectiveness
Nothing added	-	X
Hydroquinone	1.0	Δ
Copaiba extract	0.1	O
Copaiba extract	1.0	O
Copaiba extract	10.1	◎

[0021] The Copaiba extracts in Table 2 were obtained by heating reduction of the entire plant in ethanol, after which the material was filtered, concentrated and dried.

[0022] As should be clear from Table 2, the effects after exposure to sunlight were found to be that addition of Copaiba extract prevented excessive deposition of melanin pigment and prevented development of black color.

[0023]
Example 1, Cream

(Formulation)

Stearic acid	5.0 weight %
Stearyl alcohol	4.0
Isopropyl myristate	18.0
Glycerol monostearic acid esters	3.0
Propylene glycol	10.0
Copaiba methanol extract	0.01
Potassium hydroxide	0.2
Sodium hydrogensulfite	0.01
Preservative	suitable quantity
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation Method) Propylene glycol, Copaiba methanol extract and potassium hydroxide were added to and dissolved in ion exchange water and the solution was heated and maintained at 70°C (aqueous phase). The other constituents were mixed, fused by heating and maintained at 70°C (oleaginous phase). The oleaginous phase was gradually added to the aqueous phase, and, after addition of the total quantity had been completed, that temperature was maintained for a short period, with a reaction being brought about. Following that, it was uniformly emulsified with an homogenizer and was cooled to 30°C while it was being thoroughly stirred.

[0024]
Example 2; Cream

(Formulation)

Stearic acid	2.0 weight %
Stearyl alcohol	7.0
Hydrogenated lanolin	2.0
Squalane	5.0
2-octyl dodecyl alcohol	6.0
Polyoxyethylene (25 mol) cetyl alcohol ether	3.0
Glycerol monostearic acid ester	2.0
Propylene glycol	5.0
Copaiba ethanol extract	0.05
Sodium hydrogensulfite	0.03
Ethylparaben	0.3
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation Method) Propylene glycol was added to ion exchange water, heated and maintained at 70°C (aqueous phase). The other constituents were mixed, heated, fused and maintained at 70°C (oleaginous phase). The oleaginous phase was added to the aqueous phase, preparatory emulsification and then uniform emulsification were performed with an homogenizer, after which the product was cooled to 30°C as it was being thoroughly stirred.

[0025]
Example 3; Cream

(Formulation)

Solid paraffin	5.0 weight %
Beeswax	10.0

Vaseline	15.0
Liquid paraffin	41.0
Glycerol monostearic acid ester	2.0
Polyoxyethylene (20 mol) sorbitan monolauric acid ester	2.0
Soap powder	0.1
Borax	0.2
Copaiba acetone extract	0.05
Copaiba ethanol extract	0.05
Sodium hydrogensulfite	0.03
Ethylparaben	0.3
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation Method) Soap powder and borax were added to the ion exchange water and they were heated, fused and maintained at 70°C (aqueous phase). The other constituents were mixed, heated and fused and maintained at 70°C (oleaginous phase). The oleaginous phase was added to the aqueous phase as the materials were being stirred and a reaction was performed. After the reaction was completed, the product was uniformly emulsified with an homogenizer. After emulsification, it was cooled to 30°C as it was being stirred.

[0026]

Example 4; Emulsion

(Formulation)

Stearic acid	2.5 weight %
Cetyl alcohol	1.5
Vaseline	5.0
Liquid paraffin	10.0
Polyoxyethylene (10 mol) monooleic acid ester	2.0
Polyethylene glycol 1500	3.0
Triethanolamine	1.0
Carboxyvinyl polymer	0.05
(brand name: Carbopol, B.F.Goodrich Chemical Company)	
Copaiba ethyl acetate ester extract	0.01
Sodium hydrogensulfite	0.01
Ethylparaben	0.3
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation Method) Carboxyvinyl polymer was dissolved in a small quantity of ion exchange water (Phase A). Polyethylene glycol 1500 and triethanolamine were added to the remaining ion exchange water and they were heated and fused and maintained at 70°C (aqueous phase). The other constituents were heated and fused and maintained at 70°C (oleaginous phase). The oleaginous phase was added to the aqueous phase and preliminary emulsification was performed. Phase A was added and uniform emulsification was performed with an homogenizer. After emulsification, the product was cooled to 30°C as it was being stirred.

[0027]

Example 5; Emulsion

(Formulation)

Microcrystlline wax	1.0 weight %
Beeswax	2.0
Lanolin	20.0
Liquid paraffin	10.0
Squalane	5.0
Sorbitan sesquioleic acid ester	4.0
Polyoxyethylene (20 mol) sorbitan monooleic acid ester	1.0
Propylene glycol	7.0
Copaiba acetone extract	10.0
Sodium hydrogensulfite	0.01
Ethylparaben	0.3
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation Method) Propylene glycol was added to the ion exchange water, heated and maintained at 70°C (aqueous phase). The other constituents were mixed and heated and fused and maintained at 70°C (oleaginous phase). Water was gradually added as the oleaginous phase was being stirred and uniform emulsification was performed with an homogenizer. After emulsification, the product was cooled to 30°C as it was being stirred.

[0028]

Example 6; Jelly

(Formulation)

95% Ethyl alcohol	10.0 weight %
Dipropylene glycol	15.0
Polyoxyethylene (50 mol) oleyl alcohol ether	2.0
Carboxyvinyl polymer	1.0
(brand name: Carbopol 940, B.F. Goodrich Chemical Company)	
Sodium hydroxide	0.15
L-arginine	0.1
Copaiba 50% ethanol aqueous solution extract	7.0
Sodium 2-hydroxy-4-methoxybenzophenone sulfonate	0.05
Ethylenediamine tetraacetate trisodium 2-hydrate	0.05
Methylparaben	0.2
Fragrances	suitable quantity
Ion exchange water	remainder

(Preparation Method) Carbopol 940 was dissolved uniformly in ion exchange water. Separately, Copaiba 50% ethanol aqueous solution extract and polyoxyethylene (50 mol) oleyl alcohol ether were dissolved in 95% ethanol and the solution was added to the aqueous phase. Next, the other constituents were added, after which neutralization and thickening were

effected in sodium hydroxide and L-arginine.

[0029]
Example 7; Beauty solution

(Formulation)

(Phase A)	
Ethyl alcohol (95%)	10.0 weight %
Polyoxyethylene (20 mol) octyl dodecanol	1.0
Pantothenyl ethyl ether	0.1
Copaiba methanol extract	1.5
Methylparaben	0.15
(Phase B)	
Potassium hydroxide	0.1
(Phase C)	
Glycerol	5.0
Dipropylene glycol	10.0
Sodium hydrogensulfite	0.03
Carboxyvinyl polymer	0.2
(brand name: Carbopol 940 , B.F. Goodrich Chemical Company.	
Purified water	remainder

(Preparation Method) Phase A and phase C were dissolved uniformly and phase A was added to phase C and solubilized. Next, phase B was added, after which filling was performed.

[0030]
Example 8; Pack

(Formulation)

(Phase A)	
Dipropylene glycol	5.0 weight %
Polyoxyethylene (60 mol) hardened castor oil	5.0
(Phase B)	
Copaiba methanol extract	0.01
Olive oil	5.0
Tocopherol acetate	0.2
Ethylparaben	0.2
Fragrances	0.2
(Phase C)	
Sodium hydrogen sulfite	0.03
Polyvinyl alcohol (degree of saponification, 90; degree of polymerization, 2,000)	13.0
Ethanol	7.0
Purified water	remainder

(Preparation Method) Phase A, phase B and phase C were dissolved uniformly and phase B was added to phase A and solubilized. Next, this product was added to phase C, after which filling was performed.

[0031]
Example 9; Solid foundation

(Formulation)	
Talc	43.1 weight %
Kaolin	15.0
Sericite	10.0
Zinc white	7.0
Titanium dioxide	3.8
Yellow iron oxide	2.9
Black iron oxide	0.2
Squalane	8.0
Isostearic acid	4.0
Monooleic acid POE sorbitan	3.0
Isocetyl octanoate	2.0
Copaiba ethanol extract	1.0
Preservative	suitable quantity
Fragrances	suitable quantity

(Preparation Method) The powdered constituents from the talc to the black iron oxide were thoroughly mixed with a blender, the oleaginous constituents from squalane to isocetyl octanoate, the Copaiba ethanol extract, the preservative and the fragrances were added and thoroughly kneaded in, after which filling and molding were performed.

[0032]
Example 10; Emulsified foundation (cream type)

(Formulation)	
(Powder components)	
Titanium dioxide	10.3 weight %
Sericite	5.4
Kaolin	3.0
Yellow iron oxide	0.8
Red iron oxide	0.3
Black iron oxide	0.2
(Oleaginous phase)	
Decamethyl cyclopentasiloxane	11.5
Liquid paraffin	4.5
Polyoxyethylene modified dimethyl polysiloxane	4.0
(Aqueous phase)	
Purified water	50.0
1,3-butylene glycol	4.5
Copaiba ethanol extract	1.5
Sorbitan sesquioleic acid ester	3.0
Preservative	suitable quantity
Fragrances	suitable quantity

(Preparation Method) The aqueous phase was heated and stirred, after which the powered constituents, which had been thoroughly mixed and pulverized, were added and the mixture was treated with an homogenizer. The oleaginous phase, which had been heated and mixed, was added and was treated with an homogenizer, after which the fragrances were added as the mixture was being stirred and was then cooled to room temperature.

[0033]

[Effect of the Invention] As has been described above, the topical skin agent of this invention is a topical skin agent that has a melanin production inhibiting action, that has superior effects in color lightening and beautifying-whitening of pigment deposition after sunburn, blotches, freckles and melasma and that exhibits excellent safety.

[matter below line on page (7)]

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